A STUDY OF EVALUATION OF CAUSES OF HYPONATREMIA AND CORRELATION WITH BASAL CORTISOL LEVELS

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CERTIFICATE

This is to certify that this dissertation titled **"A STUDY OF EVALUATION OF CAUSES OF HYPONATREMIA AND CORRELATION WITH BASAL CORTISOL LEVELS"** submitted by **Dr.A.THIRUMURUGANANTH** to the faculty of General Medicine, **The Tamil Nadu Dr.M.G.R.Medical University, Chennai** in partial fulfillment of the requirement for the award of MD degree branch I General Medicine, is a bonafide research work carried out by him under our direct supervision and guidance.

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DECLARATION

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CONTENTS

Abstract:

Objective: To determine the etiology of hyponatremia in patients admitted to GRH and correlation with serum cortisol levels.

Study Design: Observational study involving 50 in patients who have serum sodium levels less than 130 meq/L for a period of 1 year.

Results: Mean age of the patients - 52.5 years. 18% had severe hyponatremia. 48% of males had raised cortisol values as against 17% of females. Only 34% of patients had raised cortisol values. Hypervolemia was seen in 46%, Euvolemia in 32%, hypovolemia in 22%, 78% of patients showed hypo osmolality. Mean serum sodium values were found to be 123meq/L.

Conclusion: Chronic kidney disease, Respiratory causes, fever and acute gastroenteritis were the most common etiologies. Cortisol levels were not found to be significantly elevated in patients with hyponatremia.

INTRODUCTION

Hyponatremia is the most common electrolyte disorder among hospitalized patients[26] and has been associated with increased mortality ranging from 5% to 50%, depending on severity and acuity of onset. Its prevalence among non-hospitalized elderly patients has been estimated to be between 7-11.4%, increasing to 11-22.5% among hospitalized patients.[26]

A study done by Kende M et al in over 30,000 patients over two years observed that hyponatremia was higher among medical and pediatric patients. Various studies have indicated that elderly patients showed a higher predisposition to develop hyponatremia. Natkunam et al observed that majority of patients developed hyponatremia during their hospital stay. Various studies have emphasized the susceptibilities of hospitalized elderly patients to hyponatremia.

REVIEW OF LITERATURE

Sodium and Water

Water is the most abundant constituent in the body, accounting for 50% of body weight in women and 60% in men. Total body *water* is distributed in two major compartments: 55-75% is intracellular [intracellular fluid (ICF)], and 25-45% is extracellular fluid (ECF)]. ECF is subdivided into intravascular plasma water and extra vascular (interstitial) spaces in a ratio of 3:1. Fluid movement between the intravascular and interstitial *spaces* occurs across the capillary wall and is determined by Starling forces, i.e., capillary hydraulic pressure and colloid osmotic pressure. The transcapillary hydraulic pressure gradient creeds the corresponding oncotic pressure gradient, thus favoring the movement of plasma ultrafiltrate into the extravascular space. The return of fluid into the intravascular compartment occurs via lymphatic flow.

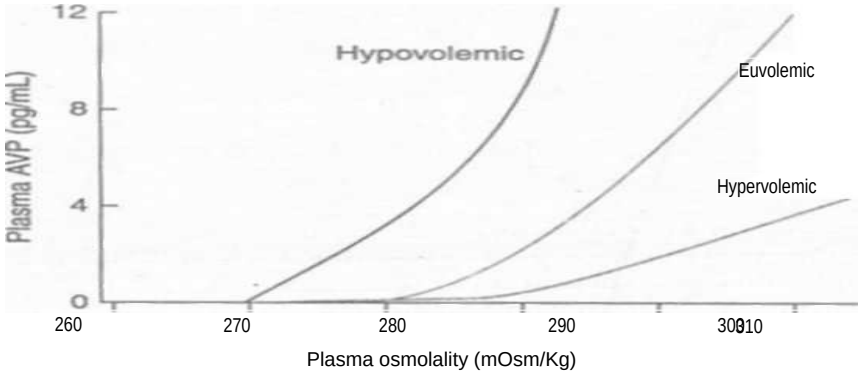
The solute or particle concentration of a fluid is known as its osmolality and is expressed as milliosmoles per kilogram of water (mosmol/kg). Water easily diffuses across most cell membranes to achieve osmotic equilibrium (ECF osmolality = ICF osmolality). Notably, the extracellular and intracellular solute compositions differ considerably

owing to the activity of various transporters, channels, and ATP-driven membrane pumps. The major ECF components are Na+ and its accompanying anions Cl^- and $HC0_3^-$, whereas K' and organic phosphate esters (ATP, creatine phosphate, and phospholipids) are the predominant ICF osmoles. Solutes that are restricted to the ECF or the ICF determine the tonicity or effective osmolality of that compartment. Certain solutes, particularly urea, do not contribute to water shifts across most membranes and are thus known as ineffective osmoles.

Water Balance

Vasopressin secretion, water ingestion, and renal water transport collaborate to maintain human body fluid osmolality between 280 and 295 mosmol/kg. Vasopressin (AVP) is synthesized in magno-cellular neurons within the hypothalamus; the distal axons of those neurons project to the posterior pituitary or neurohypophysis, from which AVP is released into the circulation. A network of central osmoreceptor neurons that includes the AVP-expressing magnocelllular neurons themselves sense circulating osmolality via nonselective, stretch-activated cation channels. These osmoreceptor neurons are activated or inhibited by modest increases and decreases in circulating osmolality, respectively; activation leads to AVP release and thirst.

AVP secretion is stimulated as systemic osmolality increases above a threshold level of -285 mosmol/kg, above which there is a linear relationship between osmolality and circulating AVP. Thirst and thus water ingestion also are activated at 285 mosmol/kg, beyond which there is an equivalent linear increase in the perceived intensity of thirst as a function of circuiting osmolality. Changes in blood volume and blood pressure are also direct stimuli for AVP release and thirst, albeit with a less sensitive response profile. Of perhaps greater clinical relevance to the pathophysiology of water homeostasis, ECF volume strongly modulates the relationship between circulating osmolality and AVP release so that *hypovolemia* reduces the osmotic threshold and increases the slope of the response curve to osmolality; *hypervolemia* has the opposite effect, increasing the osmotic threshold and reducing the slope of the response curve. Notably, AVP has a half-life in the circulation of only 10-20 min; thus, changes in extracellular fluid volume and/or circulating osmolality can affect water homeostasis rapidly. In addition to volume status, a number of nonosmotic stimuli have potent activating effects on osmosensitive neurons and AVP release, including nausea, intracerebral angiotensin II, serotonin, and multiple drug.



Circulating levels of vasopressin (AVP) in response to changes in osmolality

The excretion or retention of electrolyte-free water by the kidney is modulated by circulating AVP. AVP acts on renal V_2-type receptors in the thick ascending limb of Henle and principal cells of the collecting duct (CD), increasing cyclic adenosine monophosphate (AMP) and activating protein kinase A (PKA)-dependent phosphorylation of multiple transport proteins. The AVP- and PKA-dependent activation of Na+-Cl^- and K^+ transport by the thick ascending limb of the loop of Henle (TALH) is a key participant in the counter-current mechanism. The countercurrent mechanism ultimately increases the interstitial osmolality in the inner medulla of the kidney, driving water absorption across the renal collecting duct. However, water, salt, and solute transport by both proximal and distal nephron segments participates in the renal concentrating mechanism. Water transport across apical and basolateral aquaporin-1 water channels in the descending thin limb of the loop of Henle is thus involved, as is passive

absorption of Na^+-Cl^- by the thin ascending limb, via apical and basolateral CLC-K1 chloride channels and paracellular Na^+ transport. Renal urea transport in turn plays important roles in the generation of the medullary osmotic gradient and the ability to excrete solute-free water under conditions of both high and low protein intake.

AVP-induced, PKA-dependent phosphorylation of the aquaporin-2 water channel in principal cells stimulates the insertion of active water channels into the lumen of the collecting duct, resulting in to excrete hypertonic, concentrated urine (osmolality of up the 1200 mosmol/kg). In the absence of circulating AVP, insertion of aquaporin-2 channels and water absorption across the collection duct are essentially abolished, resulting in secretion of a hypotonic dilute urine (osmolality as low as 30-50 mosmol/kg). Abnormalities in this final common pathway are involved in most disorders water homeostasis, e.g., a reduced or absent insertion of action aquaporin-2 water channels into the membrane of principal cells in diabetes insipidus

MAINTENANCE OF ARTERIAL CIRCULATORY INTEGRITY

Sodium is actively pumped out of cells by the Na^+, K^+-ATPase membrane pump. In consequence, 85-90% of body Na^+ is extracellular and the extracellular fluid volume (ECFV) is a function of total body Na^+ content. Arterial perfusion and circulatory integrity in turn, is determined

by renal Na^+ retention or excretion, in addition to the modulation of systemic arterial resistance. Within the Kidney Na+ is filtered by the glomeruli and then sequentially reabsorption by the renal tubules. The Na^+ cation typically is reabsorbed with the chloride anion (CI^-); thus, chloride homeostasis also affects ECFV. On a quantitative level, at a glomerular filtration rate (GFR of 180 L/d and serum Na^+ of 140 mEq/L, the kidney filters some 25,200 mmol/d of Na^+-. This is equivalent to l.5 kg of salt, which would occupy roughly 10 times the extracellular space; 99.6% of Lumen filtered Na^+-Cl- must be reabsorbed to excrete 100 mM per ***day.*** Minute changes in renal Na+-Cl^- excretion will thus have significant effects on the ECFV, leading to edema syndromes or hypovolemia.

Approximately two-thirds of filtered Na^+-Cl^- is reabsorbed in the renal proximal tubule via both paracellular and transcellular mechanisms. The TALH subsequently reabsorbs another 25-30. of filtered Na+-Cl- via the apical, furosemide-sensitive Na^+-K^+-2cl cotransporter. The adjacent aldosterone-sensitive distal nephron which encompasses the distal convoluted tubule (DCT), connecting tubule (CNT), and collecting duct, accomplishes the "fine-tuning of renal Na^+- Cl^- excretion. The thiazide-sensitive Na^+ co transporter (NCC) reabsorbs 5-10% of filtered Na^+-Cl- in the DCT. Principal cells in the CNT and CD reabsorb Na^+ via, electrogenic amiloride-sensitive epithelial Na+ channels (ENaC); CI" ***ions*** are

reabsorbed primarily by adjacent intercalated cells via apical: Cl^- exchange (Cl'-OH" and Cl-HCO_3- exchange, mediated by SLC26A4 anion exchanger).

Renal tubular reabsorption of filtered Na^+-Cl- is regulated by multiple circulating and paracrine hormones in addition to activity of renal nerves. Angiotensin II activates proximal Na+Cl^- reabsorption, as do adrenergic receptors under the influence of renal sympathetic innervations; locally generated dopamine, in contrast has a natriuretic effect. Aldosterone primarily activates Na+- its reabsorption within the aldosterone-sensitive distal nephron. in particular, aldosterone activates the ENaC channel in principal cells, inducing Na^+ absorption and promoting K+ excretion.

Circulatory integrity is critical for the perfusion and function of vital organs. Underfilling of the arterial circulation is sensed by ventricular and vascular pressure receptors, resulting in a neuro humoral activation (increased sympathetic tone, activation of the renin–angiotensin - aldosterone axis, and increased circulating AVP that synergistically increases renal Na^+-Cl^- reabsorption, causes resistance, and renal water reabsorption. This occurs in the context of decreased cardiac output, as occurs in hypovolemic states, low output cardiac failure, decreased oncotic pressure, and/or increased capillary permeability. Alternatively, excessive arterial vasodilation results in *relative* arterial underfilling, leading to

neurohumoral activation in the defense of tissue perfusion. These physiological responses play important roles in many of the disorders. In particular, it is important to appreciate that AVP functions in the defence of circulatory integrity; in during vasoconstriction, increasing sympathetic nervous system Tone, increasing renal retention of both water and Na+, Cl concomitant activation of V2 receptors in the kindey can result in renal water retention and Hyponatremia.

HYPONATREMIA

Hyponatremia is defined as serum sodium lower than 135mmol/litre, which is a common condition in hospital settings and is increasingly recognized in outpatients. Hyponatremia can be asymptomatic, although careful neurological evaluation has detected subtle abnormalities in patients with chronic hyponatremia and serum sodium as high as 132 mmol/litre. At the other end of the spectrum, presentation with hyponatremic encephalopathy (central nervous system symptoms secondary to cerebral edema) is a medical emergency that must be diagnosed promptly and treated quickly, or death or devastating neurological complications can result.[17]

The cause of hyponatremia can be divided into those in which water excretion is abnormal and those in which water excretion is normal but water ingestion is considerably increased.

Causes of Hyponatremia

Hyponatremia with hypo osmolality

Impaired water excretion (UOsm > 100mOsm/Kg and usually < 300 mOsm / Kg)

Hypovolemic states

True volume depletion (by gastrointestinal, skin, or renal losses

Edematous states with reduced effective arterial blood volume

- Congestive heart failure
- Renal failure
- Cirrhosis

Diuretics (particularly thiazides)

Pain

Endocrine deficiencies (hypothyroidism and hypoadrenalism)

Syndrome of inappropriate antidiuretic hormone secretion

Cerebral salt wasting

Reduced solute intake (tea-and-toast diet, beer drinkers hyponatremia)

Normal Water excretion (Uosm > 100mOsm / Kg)

Primary polydipsia

Psychiatric disorders (particularly with phenothiazines)

Hypothalamic disorders

Hyponatremia without hypoosmolality

Normal Posm

Pseudohyponatremia (hypertriglyceridemia, hyperproteinemia genitourinary tract irrigation)

Increased Posm

Hyperosmolar hyponatremia (hyperglycemia, mannitol infusion in renal failure)

Azotemia (effective osmolaity is reduced)

HYPOVOLEMIC HYPONATREMIA

A fall in effective perfusion pressure stimulates release of the three hypovolemic hormones: norepinephrine (which redirects blood flow away from the kidneys toward the brain and heart), angiotensin II (which enhances renal Na^+ retention both directly and by promoting aldosterone release), and ADH (2). Hypovolemic hyponatremia can occur in states of dehydration or in edematous individuals with congestive heart failure (CHF) or advanced liver disease because each of these conditions is associated with a reduced effective arterial blood volume. As discussed previously, the resulting increase in the Uosm (e.g., to 600mOsm per kg) would limit renal water excretion on a 900 mOsm per day diet to 1.5L., assuming all of the ingested solute were excreted (900 mOsm per kg 600).

Solute excretion tends to be reduced in these settings, which are characterized by enhanced tubular salt reabsorption. In addition, most stimuli that activate angiotensin II release also stimulate thirst and lead to increased water ingestion, despite concurrent hypo osmolality.

DIURETIC – INDUCED HYPONATREMIA[2]

The ability to excrete a dilute urine is impaired by diuretics, whether they act in the thick ascending limb of Henle (loop diuretics) or in the distal tubule (thiazide – type diuretics). Each class reduces salt transport out of the diluting segment, thus raising the minimum achievable Uosm from 50 to approximately 250m Osm per kg, even in the absence of ADH. Reducing the minimum Uosm to this level, however, does not usually lead to hyponatremia because a large volume of urine can still be excreted by most patients. Almost all cases of diuretic –induced hyponatremia have been caused by thiazide-type other than loop diuretics. Loop diuretics which act in outer medulla, reduce the solute concentration in the renal medullary interstitium whereas ADH permits water reabsorption from the collecting tubule. By comparison, thiazide diuretics which act in cortex, impair diluting capacity but have a lesser effect on concentrating ability. For reasons that are not well understood, however most individuals with thiazide induced hyponatremia gain weight, indicating that hyponatremia is a part of increased water intake.

ADVANCED RENAL FAILURE

The normal glomerular filtration rate (GFR) is approximately 180L per day. As renal function decreases, the ability to excrete water also decreases. The limitation in water excretion occurs for two reasons: tubular dysfunction leads to an inability to dilute the urine maximally, even in the absence of ADH. The drop in GFR, particularly when severe, reduces daily solute excretion.

ENDOCRINE DEFICIENCY

Hypothyroidism and hypocortisolism can impair water excretion. Both may reduce cardiac output or stroke volume, leading to increased ADH release the resulting fall in GFR adversely affects free water excretion diminishing delivery of filtrate to the diluting segments. Decreased delivery may be particularly important in patients with myxedema in whom hyponatremia may develop despite appropriate suppression of ADH release.

Another factor contributing to the hyponatremia of hypocortisolism is that corticotrophin-releasing factor promotes the release of adrenocorticotropic hormone (ACTH) and ADH, although the reason for the concomitant release of these hormones is not known. It is important to note that adrenocortical dysfunction (as in Addision's disease) leads to

reduced cortisol and aldosterone levels, the latter predisposing to hyperkalemia. The presence of a low cortisol level alone, due to either pituitary or hypothalamic disease, or the abrupt withdrawal from prolonged exogenous corticosteroid administration may cause hyponatremia but should not alter potassium homeostais, because aldosterone release is normal.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION:

The syndrome of inappropriate ADH secretion (SIADH) is characterized by the following. Plasma hypoosmolality, Uosm Above 100 to 150 mOsm per kg; urinary Na^+ concentration above 20mEq per L, reflecting normal renal perfusion; normal adrenal, renal, and thyroid function; and normal potassium and acid-base balance. SIADH may be caused by enhanced hypothalamic ADH secretion, ectopic hormone production (usually by cancer), potentiation of ADH effect (as with chlorpropamide), or administration of medications with ADH activity.

This disorder has been described in patients with hypovolemia, psychosis, and chronic malnutrition, and in normal pregnancy (in which the plasma Na^+ concentration decreases by the second trimester from 140 to 135mEq per L). ADH release is not suppressed until the Posm falls well below normal in this disorder.

An increasingly common cause of hyponatremia is symptomatic human immunodeficiency virus (HIV) infection[3]. Although hyponatremia in HIV-infected patients may result from volume deficiency or adrenal insufficiency, may patients have SIADH. Pneumonia due to *Pneumocystis jiroveci* or other organisms, central nervous system infections, and malignant disease are most often responsible in this setting.

CEREBRAL SALT WASTING[4]

Cerebral salt wasting is a rare disorder characterized by a low $P_{Osm,}$ a U_{Osm} above 100 to 150 mOsm per kg and a urine Na+ Concentration greater than 20mEq per L. Unlike SIADH, however, evidence of volume depletion (including low central filling pressures) is present. In affected individuals, therefore, the high urinary Na+ represents inappropriate salt wasting rather than a response to normal tissue perfusion (as in SIADH patients).

REDUCED SOLUTE INTAKE

As noted, a reduction in salt and protein intake can lead to hypoosmolality if water intake exceeds output. Severely reduced solute intake, as occurs with a tea-and-toast diet, can cause hyponatremia even with normal degrees of water intake. “Beer drinkers hyponatremia” occurs for a similar reason: the limited amount of solute in beer relative to its water content may be inadequate to permit excretion of that water. In both

conditions, the U_{Osm} less than 100 mOsm per kg). The absence of polyuria and the development of hyponatremia with normal or slightly above normal fluid intake distinguish these individuals from those with primary polydipsia

HYPOOSMOLAR DISORDERS WITH NORMAL WATER EXCRETION

Psychiatric patients, particularly those with schizophrenia, often have abnormalities in water balance. Evaluation of psychotic patients has revealed that a variety of defects in water handling can occur that affect thirst, the release of ADH, and the renal response to ADH. Depending on the abnormality that is present, the patient may present with polydipsia and polyuria or hyponatremia

Hyponatremia has been reported in as many as 13% of marathon runners, and may occasionally be fatal. Although the exact mechanism has not been elucidated, risk factors for developing low serum sodium levels include weight gain during the race, female sex, racing time, and lower body mass indeed.[5]

PRIMARY POLYDIPSIA

Many chronically psychotic patients have moderate-to-marked increase in water intake. This may be manifested clinically by exaggerated weight gain during the day associated with a transient reduced in plasma sodium concentration.

Drug therapy may contribute to the increase in water intake to schizophrenic patients Many antipsychotic drugs induce the sensation of a dry mouth which enhance sensation of thirst.

Because people with normally functioning kidneys and regulation of ADH secretion are capable of excreting more than 10 to 15 L of urine per day, hyponatremia has developed even though the U_{osm} was appropriately dilute. More commonly however polydipsic patients manifesting hyponatremia have a concurrent abnormality in ADH release or response. Concurrent thiazide diuretic therapy for systemic hypertension can lead to the marked and symptomatic reduction in the plasma sodium concentration in these patients

HYPONATREMIA WITHOUT HYPO OSMOLALITY

Hyponatremia may occur without plasma hypoosmolality. An increase in the plasma concentration of proteins or lipids (primarily

triglyceride in lipemic plasma) can reduce the plasma Na+ concentration. Lipids and proteins displace water from a given volume of plasma but do not affect the Na+ concentration in the water phase of plasma. As a result, the measured P_{osm} is normal in this condition, which is called ***pseudohyponatremia***[17]**.** Because sodium concentration in the aqueous component of plasma is normal, this form of hyponatremia is not of pathophysiological consequence.

There are instances in which patients with plasma hyperosmolality may develop hyponatremia. This most commonly occurs with severe hyperglycemia or when mannitol is given to patients with renal failure resulting in osmotic shift of water from cells into ECF fluid diluting the plasma Na^+ concentration. For every 100mg per dL of rise in blood sugar, plasma Na^+ concentration falls by 1.6mEq per L.[6]

SYMPTOMS OF HYPONATREMIA

A variety of symptoms may be found including lethargy, confusion, nausea, vomiting and in severe cases seizures and coma. Focal neurologic symptoms are uncommon.

PATHOPHYSIOLOGY OF CORTISOL PRODUCTION

The adrenal cortex produces three classes of corticosteroid hormones: glucocorticoids (e.g., Cortisol), mineralocorticoids (e.g., aldosterone), and adrenal androgen precursors (e.g., dehydroepi-androsterone, DHEA) Glucocorticoids and mineralocorticoids act through specific nuclear receptors, regulating aspects of the physiologic stress response as well as blood pressure and electrolyte homeostasis.

Production of glucocorticoids and adrenal androgens is under control of the hypothalamic–pituitary–adrenal (HPA) axis, whereas mineralocorticoids are regulated by the renin angiotensin Aldosterone (RAA) system.

Glucorticoid synthesis is under inhibitory feedback control of hypothalamus and the pituitary hypothalamic release of corticotropin-releasing hormone (CRH) occurs in response to endogenous or exogenous stress. CRH stimulates the cleavage of the 241-amino acid polypeptide pro opiomelanocortin (POMC) by pituitary-specific prohormone convertase, yielding adrenocorticotropic hormone (ACTH). ACTH is released by the corticotrope cells of the anterior pituitary and **acts as** the pivotal regulator of **Cortisol** synthesis, with additional short-term effects on mineralocorticoid and adrenal androgen synthesis. The release of CRH, and

subsequently ACTH, occurs in a pulsatile fashion that follows a circadian rhythm under the control of the hypothalamus, specifically its suprachiasmatic nucleus (SCN), with additional regulation by a complex network of cell-specific clock genes. Reflecting the pattern of ACTH secretion, adrenal Cortisol secretion exhibits a distinct circadian rhythm, with peak levels in the **morning** and low levels in the evening.[8]

Cortisol is inactivated to cortisone by the microsomal enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) mainly in the kidney, but also in the colon, salivary glands, and other target tissues. Cortisol and aldosterone bind the mineralocorticoid receptor (MR) with equal affinity; however, Cortisol circulates in the bloodstream at about a thousand fold higher concentration. Thus, only the rapid inactivation of Cortisol to cortisone by 11β-HSD2 prevents MR activation by excess Cortisol, thereby acting as a tissue-specific modulator of the MR pathway. In addition to Cortisol and aldosterone, deoxycorticosterone (DOC) also exerts mineralocorticoid activity. DOC accumulation due to 11β-hydroxylase deficiency or due to tumor-related excess production can result in mineral corticoid excess.[22]

DIAGNOSTIC EVALUATION OF HYPONATREMIA [22]

Clinical assessment of hyponatremic patients should focus on the underlying cause; a detailed drug history is particularly crucial. A careful clinical assessment of volume status is obligatory for the classical diagnostic approach to hyponatremia. Hyponatremia is frequently multifactorial, particularly when severe; clinical evaluation should consider all the possible causes for excessive circulating AVP, including volume status, drugs, and the presence of nausea and/or pain. Radiologic imaging also may be appropriate to assess whether patients have a pulmonary or CNS cause for hyponatremia. A screening chest X-ray may fail to detect a small cell carcinoma of the lung; CT scanning of the thorax should be considered in patients at high risk for this tumor, e.g., patients with a history of smoking.

Laboratory investigation should include a measurement of serum osmolality to exclude pseudohyponatremia, which is defined as the coexistence of hyponatremia with a normal or increased plasma tonicity. Most clinical laboratories measure plasma Na+ concentration by testing diluted samples with automated ion-sensitive electrodes, correcting for this dilution by assuming that plasma is 93% water; this correction factor can be inaccurate in patients with pseudohyponatremia due to extreme hyperlipidemia and/ or hyperproteinemia, in whom serum lipid or protein

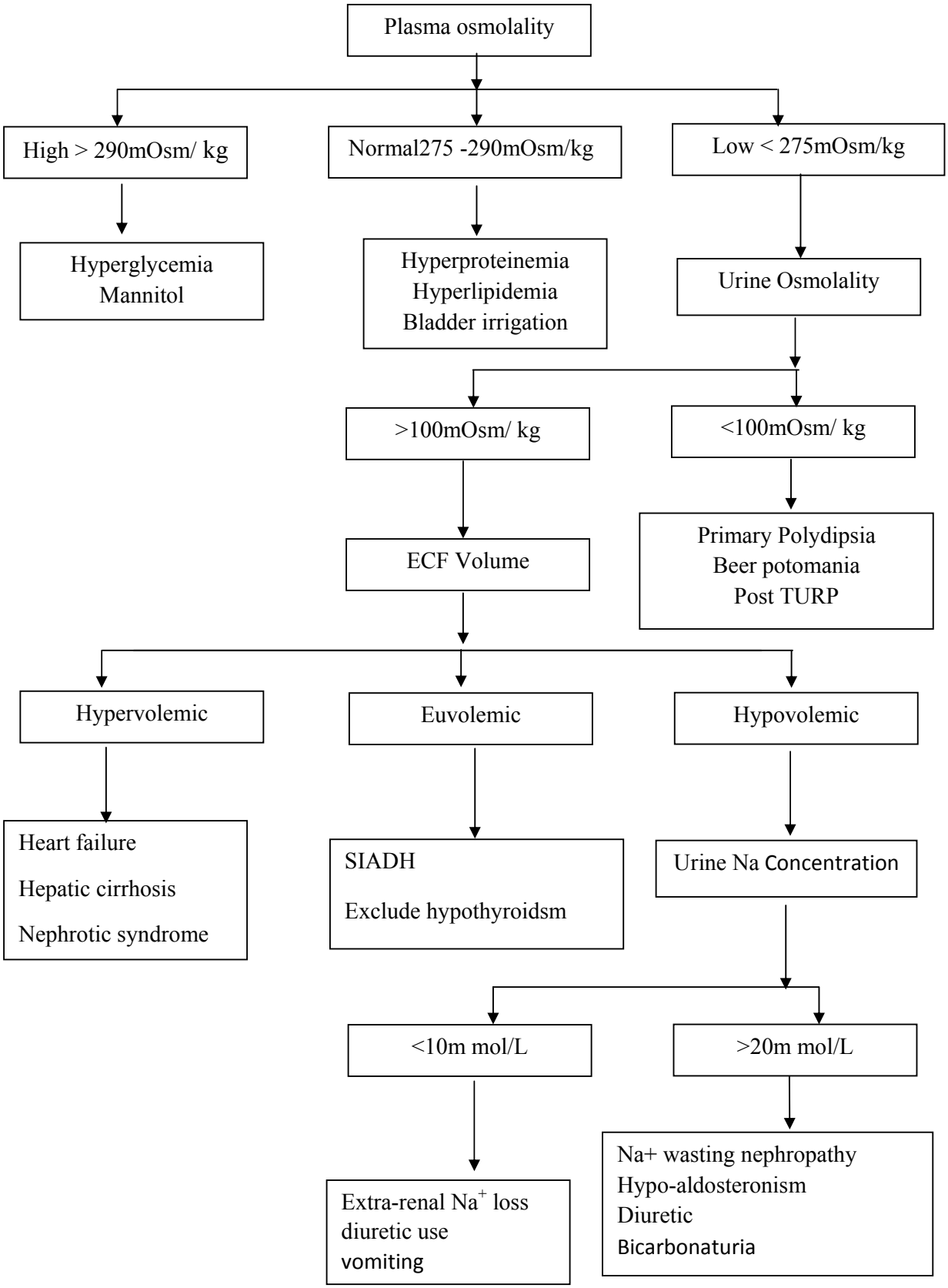
makes up a greater percentage of plasma volume. The measured osmolality also should be converted to the effective osmolality (tonicity) by subtracting the measured concentration of urea (divided by 2.8 if in mg/dL); patients with hyponatremia have an effective osmolality <275 mosmol/kg.

Elevated BUN and creatinine in routine chemistries also can indicate renal dysfunction as a potential cause of hyponatremia, whereas hyperkalemia may suggest adrenal insufficiency or hypoaldosteronism. Serum glucose also should be measured; plasma Na+ concentration falls by -1.6 to 2.4 mM for every 100-mg/dL increase in glucose due to glucose-induced water efflux from cells; this "true" hyponatremia resolves after correction of hyperglycemia. Measurement of serum uric acid also should be performed; whereas patients with SIADH-type physiology typically will be hypouricemic (serum uric acid <4 mg/dL), volume-depleted patients often will be hyperuricemic. In the appropriate clinical setting, thyroid, adrenal, and pituitary function should also be tested; hypothyroidism and secondary adrenal failure due to pituitary insufficiency are important causes of euvolemic hyponatremia, whereas primary adrenal failure causes hypovolemic hyponatremia. A cosyntropin stimulation test is necessary to assess for primary adrenal insufficiency.

Urine electrolytes and osmolality are crucial tests in the initial evaluation of hyponatremia. A urine Na^+ concentration <20-30 mM is

consistent with hypovolemic hyponatremia in the clinical absence of a hypervolemic, Na^+-avid syndrome such as CHF. In contrast, patients with SIADH typically excrete urine with a Na^+ concentration that is >30 mM. However, there can be substantial overlap in urine Na^+ concentration values in patients with SIADH and hypovolemic hyponatremia, particularly in the elderly; the ultimate "gold standard" for the diagnosis of hypovolemic hyponatremia is the demonstration that plasma Na^+ concentration corrects after hydration with normal saline. Patients with thiazide-associated hyponatremia also may present with a higher than expected urine Na^+ concentration and other findings suggestive of SIADH; one should defer making a diagnosis of SIADH in these patients until 1-2 weeks after discontinuation of the thiazide. A urine osmolality <100 mosmol/kg is suggestive of polydipsia; urine osmolality >400 mosmol/kg indicates that AVP excess is playing a more dominant role, whereas intermediate values are more consistent with multifactorial pathophysiology (e.g., AVP excess with a significant component of polydipsia). Patients with hyponatremia due to decreased solute intake (beer potomania) typically have urine Na^+ concentration <20mM and urine osmolality in the range of < 100 to the low 200's. Finally, the measurement of urine K^+ concentration is required to calculate the urine:plasma electrolyte ratio, which is useful to predict the response to fluid restriction.

ALGORITHM TO DIAGNOSE HYPONATREMIA



AIM OF THE STUDY

1. To evaluate the common causes of Hyponatremia in patients admitted to Government Rajaji Hospital Madurai.

2. To findout if there is any correlation between serum cortisol values and low serum sodium values in our patients.

MATERIALS AND METHODS

Definition : Hyponatremia is defined as serum sodium concentration of less than 130mEq/L[16] Normal Cortisol Levels – 4.3 – 22.0μg/dl : (7 – 9 AM)[18]

Study Area : Madurai Medical College and Government Rajaji Hospital Madurai which is one of the largest Hospitals in Tamilnadu.

Study Design : Observational Study

Study Period : November 2010 to November 2011

Sample Size : 50 inpatients

Study Population

All the Inpatients both male and female who were admitted for various ailments whose biochemical values showed serum sodium to be less than 130mEq/l.(values confirmed with repeat sample)

Inclusion Criteria

i) All inpatients who were admitted both in General wards & ICU irrespective of their age / sex who showed Hyponatremia (confirmed with two consecutive low values)

Exclusion Criteria

i) Patients who were on treatment with steroids for various diseases were excluded.

ii) Female Patients who were pregnant were excluded.

Study Method

Basal cortisol levels were estimated inpatients with hyponatremia with blood samples drawn on the next day morning between 7.00 AM – 9.00 AM and results were Analysed. Other biochemical parameters like Blood Sugar, Urea, Serum Creatinine, Serum potassium were estimated. Serum osmolality was calculated with the formula given below and patients were classified.

$$\text{Serum osmolality} = 2 \times \text{serum } Na^{+} + \frac{\text{Blood Sugar (in mg/dl)}}{18} + \frac{\text{Blood Urea (mg/dl)}}{6}$$

Other clinical data like age/sex, pulse rate, Blood Pressure, Edema, Volume Status, Urine Output were also estimated.

Lab Methods

The Biochemistry lab is a standardized Laboratory. The methods used for estimation are

1. Serum Sodium - HILITE / TRANSMINASE
2. Serum Potassium - I.S.Electrode (Ionselective Electrophoresis)
3. Urea - Glutaraldehyde LDH
4. Creatinine - Jaffe Kinetic
5. Sugar - (Glucose Per Oxidase)
6. Serum Cortisol - Chemiluminescence

STATISTICAL TOOLS

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2010)** developed by Centre for Disease Control, Atlanta.

Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's chi square test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS AND ANALYSIS

TABLE 1-AGE DISTRIBUTION

Age group	Cases	
	No	%
Less than 40 years	10	20
40 – 49 years	11	22
50 – 59 years	11	22
60 -69 years	7	14
70 & above	11	22
Total	50	100
Range	20-85 years	
Mean	52.5 years	
SD	16.5 years	

Age group of patients included in the study ranged from 20 years to 85 years. Their mean age was 52.5 years and standard deviation 16.5 years.

FIGURE 1

AGE DISTRIBUTION

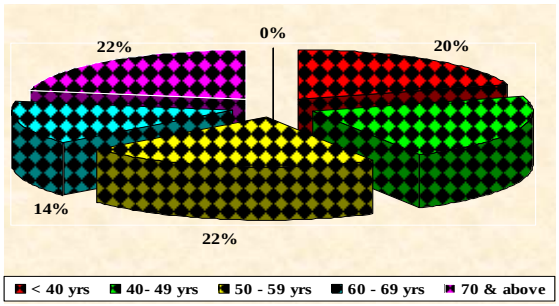


TABLE 2

AGE AND SEVERITY WISE DISTRIBUTION OF HYPONATREMIA

AGE	NUMBER	MILD(126-130meq/L)	MODERATE(120-125meq/L)	SEVERE(<120meq/L)	PERCENTAGE
12-25yrs	4	2	2	-	8
26-45yrs	14	7	4	3	28
46-64yrs	17	7	5	5	34
>=65yrs	15	7	7	1	30
TOTAL	**50**	**23(46%)**	**18(36%)**	**9(18%)**	**100**

Table 3 :
Age and serum cortisol

Cases with cortisol level	Age in years	
	Mean	SD
Increased	61.9	14.9
Not increased	47.7	15.3
'p'	0.007 Significant	

In cases where the cortisol levels increased, the age of the patients were 61.9 ±14.9 years and in the remaining group they were 47.7 ±15.3 years. This difference was statistically significant.('p' = 0.007)

FIGURE 2:
AGE & CORTISOL LEVELS

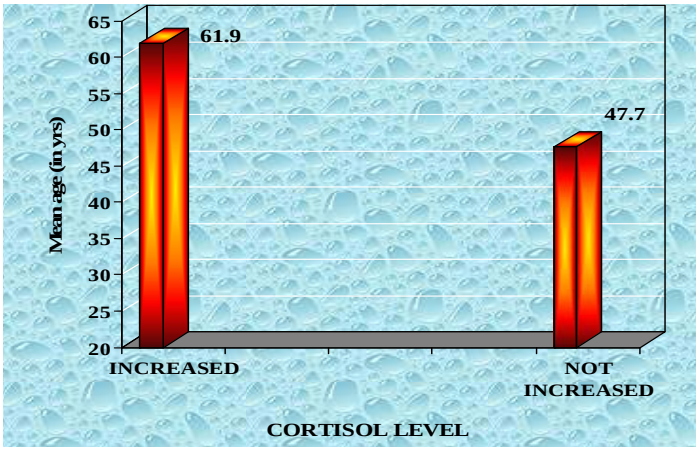


Table 4 :
Sex distribution

Age group	Cases	
	No	%
Male	27	54
Female	23	46
Total	50	100

FIGURE 3:
SEX DISTRIBUTION

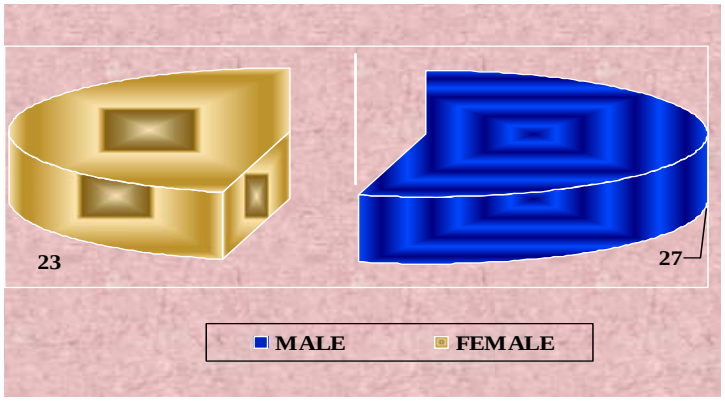


Table 5 :
Sex and serum cortisol

Sex	Serum cortisol					
	Increased		Not increased		Mean	SD
	No	%	No	%		
Male (37)	13	48.1	14	51.9	21.0	14.8
Female (23)	4	17.4	19	82.6	13.5	5.6
`p`	0.0467 Significant					

In 48.1% of males. the cortisol values increased whereas they increased only in 17.4% of females. Mean cortisol values of males (21.0) were also higher than that of females (13.5).

There was statistically significant relationship between sex of the patient and cartisol values (p = 0.0467).

FIGURE 4:
SEX & CORTISOL LEVEL

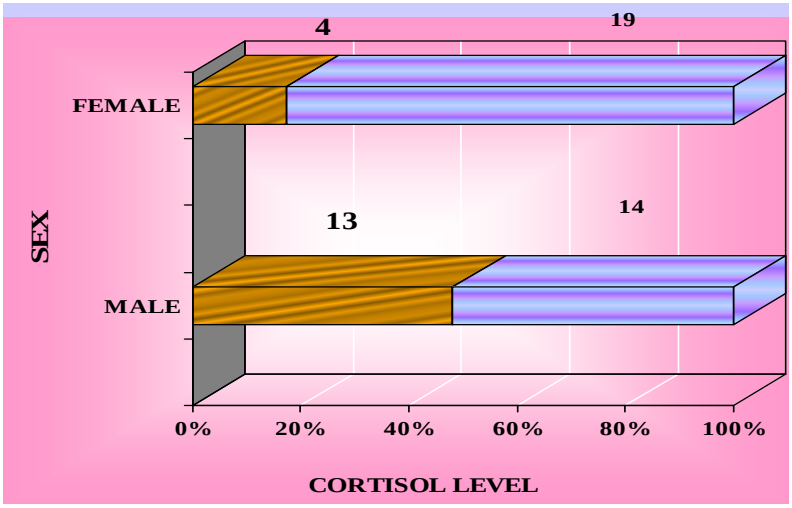


FIGURE 5:

OSMOLAR DISTRIBUTION

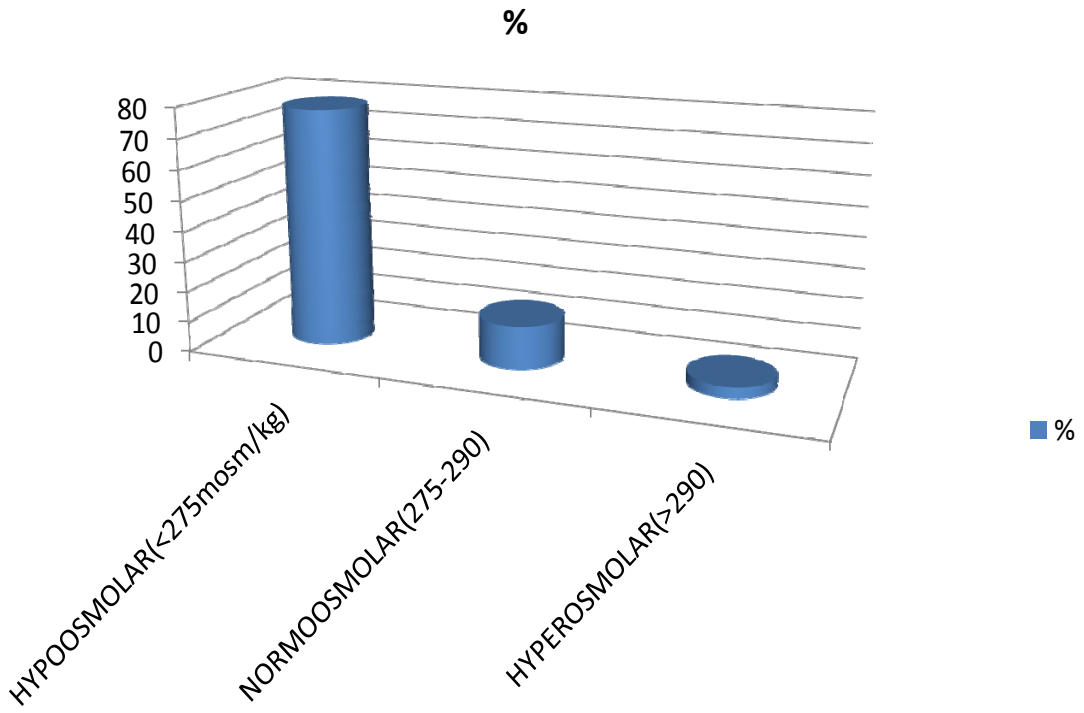


FIGURE 6:

VOLUME STATUS

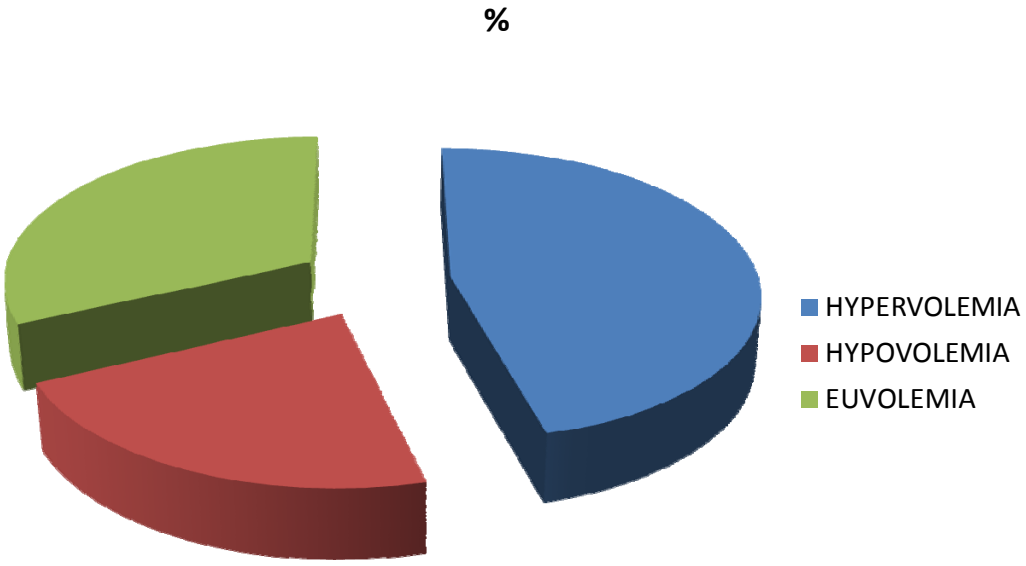


Table 6 :
Cortisol levels in Hyponatremia cases

Cortisol levels	Cases	
	No	%
Increased	17	34
Not increased	33	66
Range	0.8-63	
Mean	17.54	
SD	12.01	

In 17 (34%) hyponatremia cases, the cortisol levels increased. In the total study cases, the cortisol values were 17.54 ± 12.01.

FIGURE 7:
CORTISOL LEVELS

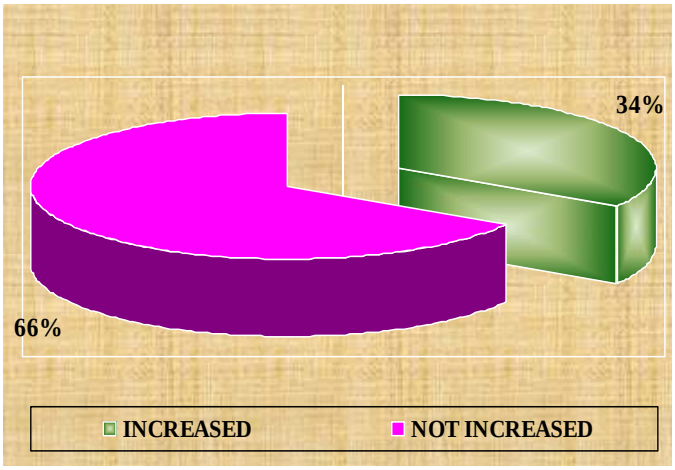


Table 7 :
Cortisol levels and Blood sugar / Urea / Sodium

Cortisol level	Blood sugar		Urea		Sodium	
	Mean	SD	Mean	SD	Mean	SD
Increased	133.5	77.9	90.8	76.9	122.8	4.4
Decreased	117.2	67.1	51.3	45.7	123.3	6.2
'p'	0.4545 Not significant		0.0276 Not significant		0.2285 Not significant	

Mean urea values were significantly higher in cases with increased cortisol levels (p = 0.0276). There was no such association in the case of blood sugar and sodium.

FIGURE 8:
CORTISOL LEVEL &
BLOOD SUGAR/ UREA / SODIUM

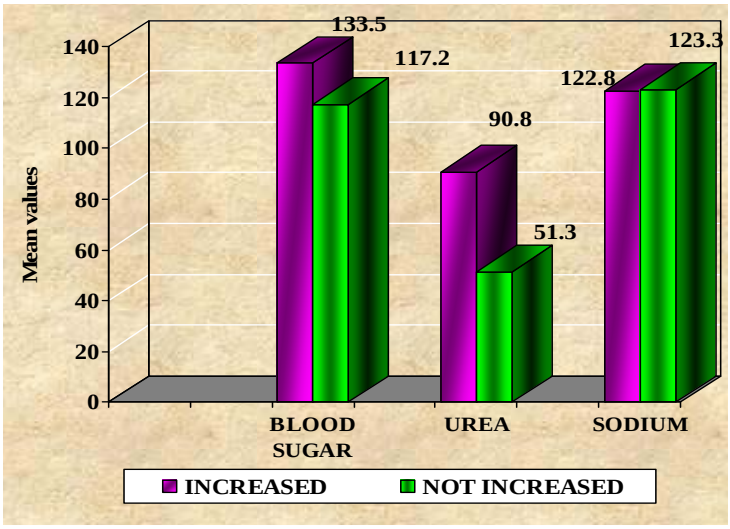


TABLE 8:
Other quantitative variables

Variable	Range	Mean	SD
Sodium	108-129	123.1	5.6
Potassium	2.2-6.9	4.04	0.91
Cortisol	0.8-6.3	17.54	12.01
Urine output (ml)	100-1300	759	265
Osmolality	226-301	264	16.7

Table 9:
Comorbidity and other risk factors

Comorbidity	Cases		
	Yes	%	
Diarrhea	3	6	
Vomiting	17	34	
Pain	23	46	
Edema	23	46	
Anaemia	26	52	
Thyroid	-	-	
Drugs	1	2	
IVF	3	6	
Diuretic	14	28	

Table 10 :
Cortisol level and Pulse Rate / Blood Pressure

Cortisol level	Pulse rate		SBP		DBP	
	Mean	SD	Mean	SD	Mean	SD
Increased	94.4	17.4	129.4	40.2	78.8	16.5
Decreased	88	11.4	126.7	31	81.2	14.9
'p'	0.2805 Not significant		0.8198 Not significant		0.8814 Not significant	

There was no significant association between pulse rate. B.P values and increase in cortisol levels.

Table 11 :
Cortisol level and Creatinine and Potassium

Cortisol level	Creatinine		Potassium	
	Mean	SD	Mean	SD
Increased	3.36	4.45	4.04	0.74
Decreased	1.69	1.66	4.04	1.0
'p'	0.0881 Not significant		0.6224 Not significant	

Creatinine and potassium values were not significantly related to increase in cortisol levels ($p > 0.05$).

TABLE 12:
PAIN AND SERUM CORTISOL

	Cortisol level				'p'
	Increased		Not increased		
	No	%	No	%	
Pain					
Yes	7	30.4	16	69.6	0.848
No	10	37	17	63	Not significant

FIGURE 9:
PAIN AND SERUM CORTISOL

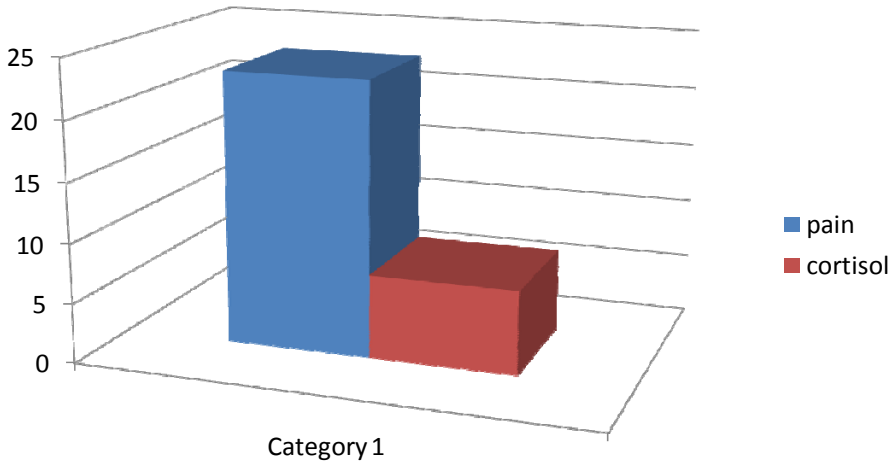


Table 13 : Cortisol levels and Comorbidity

Complications	Cortisol level				'p'
	Increased		Not increased		
	No	%	No	%	
Anaemia					
Yes	12	46.2	14	53.8	0.1119
No	5	20.8	19	79.2	Not significant
Drugs					
Yes	-	-	1	100	0.66
No	17	34.7	32	65.3	Not significant
IVF					
Yes	1	33.3	2	66.7	0.7363
No	16	34	31	66	Not significant
Diuretic					
Yes	6	42.9	8	57.1	0.3076
No	11	30.6	25	69.4	Not significant

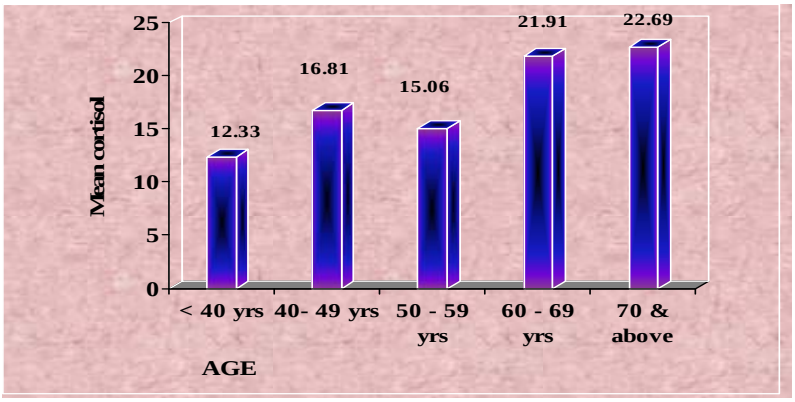
TABLE 14:
ETIOLOGIES

Dianosis	Cases	
	No	%
Chronic kidney disease	13	26
Respiratory causes	10	20
Fever	6	12
Congestive cardiac failure	5	10
Acute gastric enteritis	4	8
CNS tumours	2	4
CVA	2	4
SLE	2	4
Chronic liver disease	2	4
D.M.	2	4
Aplastic anaemia	1	2
OPC Poisoning	1	2
Total	50	100

TABLE 15:
MEAN CORTISOL LEVELS IN DIFFERENT AGE GROUPS

Age group	Cortisol	
	Mean	S.D.
Less than 40 years	12.33	6.99
40 – 49 years	16.81	17.19
50 – 59 years	15.06	7.65
60 -69 years	21 91	15 39
70 & above	22.69	9.45
Total	17.54	12.01
`p`	**0.0339** **Significant**	

FIGURE 10:
AGE AND SERUM CORTISOL



DISCUSSION

The present study included patients with serum sodium less than 130mEq/L[16]. In these, there were 27 males and 23 females in the ratio of 1.17:1. In our hospital, usually there are more number of male patients admitted than female patients. Hence this slight increase in male patients was not very significant**.(TABLE 4)**

In the present study hyponatremia is commonly seen in patients more than 45 years. Similar results were observed by Hochmann[13] and Vurgese[16] in their studies. Mean age of the patients of the present study was 52.5 years**(TABLE 1).**

This is similar to Vurgese[16] study, which showed a mean age of 57.05 years and Anderson[25] study, which showed a mean age of 58 years. The commonest age group was 45-64 years, and the least affected was 13-25 years(**TABLE 2**); which also showed similar results with Vurgese[16] study.

Based on the serum sodium concentration, the hyponatremia was classified into mild, moderate and severe, with serum sodium levels of 126-130mEq/L, 120-125mEq/L and <120 mEq/L respectively[16]. In the study by Hochman et al[13] , there were 39% of patients with mild hyponatremia and the rest of the 61% had moderate to severe hyponatremia. In the study by

Vurgese[13], 33% of the patients had mild hyponatremia and 67% of the patients had moderate to severe hyponatremia.

In our study 46% of patients had mild hyponatremia where as 54% of patients had moderate to severe hyponatremia(**TABLE 2**) which is slightly in variance with the above studies. No significance could be attached to difference in this incidence.

The hydration status of the patients were classified based on the clinical examination. They were divided into euvolemic, hypovolemic and hypervolemic states. In the present study 23 patients were hypervolemic; 11 patients were hypovolemic and 16 were euvolemic. Comparative results are shown in the below table

TYPE	**ANDERSON %**	**PRESENT STUDY %**
EUVOLEMIA	34	32
HYPERVOLEMIA	31	46
HYPOVOLEMIA	35	22

This correlated with other studies, but our study showed a slight increase in the patients with hypervolemia. This is in slight variance with other studies. This may probably be due to increased number of patients

with chronic kidney disease with volume overload status(**TABLE 14**) ;in our study similar results were obtained in patients with euvolemia status.

On further evaluation of the causes of hyponatremia in our patients, our study showed similar results to the studies done by Vurgese et al[16]

Comparative analysis of common causes in our study with Vurgese et al[16] is shown in the table below,

OUR STUDY	**VURGESE et al[16]**
Chronic kidney disease 13 (26%)	Renal failure (acute and chronic) 13 (19.6%)
Respiratory causes-10 (20%) Ca lung-2 Pneumonia-4 COPD-2 Pulmonary tuberculosis-2	SIADH(23%) due to Pneumonia-13 Drugs-2 COPD-3 Bronchiectasis -3 Bronchogenic Carcinoma-3 HIV-1
Congestive cardiac failure-5(10%)	Congestive cardiac failure-12(18%)

Acute gastro enteritis-4(8%)	Acute gastro enteritis-2(3%)
Chronic liver disease-2(4%)	Chronic liver disease-4(6%)
Diabetes mellitus-2(4%)	Diabetes mellitus-4(6%)

Due to limited resources availability the other investigations like urine osmolarity and urine sodium levels could not be estimated.

Our present study showed hypo osmolarity in 39 of 50 patients. And normal osmolarity in 7 out of 50 patients, which is similar to the results shown by studies of Devita et al[15]. the comparative results are shown in the table below

	OUR STUDY	**DEVITA MV et al**
HYPOOSMOLAR	78%	83%
NORMOOSMOLAR	14%	17%
HYPEROSMOLAR	8%	-

Many of the causes of hyponatremia have multifactorial pathophysiology. patients with congestive cardiac failure have hypervolemic hyponatremia due to salt and water retention. They also have hyponatremia due to low salt diet and diuretic therapy. Similarly patients

with diabetes mellitus have hyponatremia possibly due to associated renal failure, SIADH, due to drug therapy and also some amount of pseudo hyponatremia due to excess blood sugar causing hyperosmolar hyponatremia. In cerebrovascular accidents[22], the hyponatremia is usually due to SIADH and mannitol therapy.

Regarding the correlation of serum basal cortisol levels with hyponatremia- only 17 of the 50 patients with hyponatremia showed increase in basal cortisol levels(**TABLE 6**)

There is no significant association found with serum cortisol and low serum sodium values in our patients. This is similar to the results obtained by P.A.Mason et al[11] who showed that cortisol levels were unaffected by sodium depletion. Similar results were also obtained by F.A.O.MENDEL SOHN et al[12] who concluded that plasma cortisol was unaffected by sodium deprivation. Studies of R.Fraser et al[11] also showed similar results. Though serum cortisol has both glucocorticoid and mineralocorticoid activity, there is no significant sodium retention seen in our study. This may be probably due to the enzyme 11 beta hydroxy steroid dehydrogenase 2(11βHSD2), which selectively inactivates cortisol to cortisone, prevents mineralocorticoid receptor activation by cortisol. Aldosterone and arginine vasopressin seems to be more concerned with sodium and water homeostasis.

The average values of serum basal cortisol was 18±1.6µg/100ml in studies by F.A.O.Mendel sohn et al[12]. Our study showed an average serum cortisol levels of 17.54µg/100ml (**TABLE 6**) which is similar to the above said study.

The average age of the patients where serum cortisol was found to be increased was 61.9years in our study(**TABLE 3/ TABLE 15**) . Similar results were seen in studies by F.A.O.Mendel sohn et al[12] which showed an average age of 56years. Hence our study correlated well with other studies.

CONCLUSION

1. Our study shows chronic kidney disease with volume overload as the most common cause of hyponatremia.

2. Other common causes include respiratory causes, fever, congestive cardiac failure, acute gastro enteritis and CNS tumours.

3. Raised cortisol levels do not seem to correlate with low sodium values.

4. No significant association is seen between pulse rate, blood pressure and increase in cortisol levels.

5. Older patients seem to have higher levels of basal cortisol during the illness.

6. Mean serum sodium value was found to be 123 mEq/L in our study

BIBLIOGRAPHY

1. Adrogue HJ, Madias NE: Hyponatremia NEJM 342:1581, 2000

2. Friedmann E, shadel M, Halkin H, et al: Thiazide induced hyponatremia – Reproducibility by a single dose rechallenge and an analysis of pathogenesis Ann : Internal Medicine. 110:24, 1989.

3. Vitting K, Gardenswartz M, Zabatekis P, et al: Frequency of hyponatremia in acquired immune deficiency syndrome. JAMA 263:973, 1990.

4. Tanneau R, Pennec Y, Jouquan J, et al: Cerebral salt wasting in elderly patients. Ann. of Int.Medicine 107:120, 1987.

5. Almond CS, Shin AY, et al: Hyponatremia among runners in Boston Marathon NEJM 352:1550, 2005.

6. Katz M: Hyperglycemia – induced hyponatremia : calculation of expected Sr. Na^+ depression. NEJM 289: 843, 1973.

7. Oster JR, Singer I: Hyponatremia, hypoosmolality, and hypotonicity. Tables and Fables – Arch. Internal Medicine 159: 333, 1999.

8. Weitzmann ED Fukushima DK, Nogeire C, et al, 24 hours pattern of the episodic secretion of cortisol in normal subjects. J-clin. Endocrinology and Metabolism 1971; 71: 452-463.

9. Hypertension and the Cortisol – Cortisone shuttle – J.clin. Endocrinology and Metabolism 2003; 88:2384 – 2392.

10. The interaction of Sodium and Potassium status of ACTH and Angiotensin II in the control of cortisol secretion. J.Steroid Biochemistry Vol. 11, issue 1, part 3, 1979 by R.Fraser and PA.Mason et al.

11. The effect of sodium deprivation and of angiotensin II infusion on the peripheral plasma concentrations of 18 – hydroxycorticosterone, aldosterone and other corticosteroids in man. P.A. Mason, et al Journal of Steroid Biochemistry Vol.8, Issue 8, August 1977, Pages 799-804.

12. Renin, Angiotensin II, and Adrenal Corticosteroid Relationships during Sodium Deprivation in Normotensive and Hypertensive Man by F.A.O. Mendelsohn, et al Circulation Research (American Heart Association) 1972, 31:728-739.

13. Hyponatremia in internal medicine ward patients: causes, treatment and prognosis. Hochman I, Cabili S – Isr Med Science 1989 Feb : 25(2) : 73-6.

14. Incidence, causes and prognostic factors of hyponatremia in intensive care by Bennani SL, et al Rev Med Interne, 2003 Apr; 24(4) :224-9.

15. Incidence and etiology of hyponatremia in an intensive care unit by Devita MV, et al Clin Nephrol 1990 Oct; 34(4) : 163-6.

16. Frequency and Etiology of Hyponatremia in Adult Hospitalized Patients in Medical Wards of a General Hospital in Kuwait. Thomas Abraham Vurgese, et al Al Jahra Hospital, Kuwait – Kuwait Medical Journal 2006, 38(3) : 211-213.

17. Irwin & Rippe's intensive care Medicine.

18. Williams Text book of endocrinology 11th Edition

19. Current Medical Diagnosis and Treatment 2011.

20. Brenner and rector's - The Kidney – 7th edition.

21. Oxford Text Book of Medicine - 5th edition.

22. Harrisons Text Book of Internal Medicine – 18th edition.

23. Davidsons Text Book of Principles and Practice of Medicine– 21st edition.

24. Tintinallis Text Book of Emergency Medicine – 7th edition.

25. Anderson RJ, Chung HM, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. *Ann Intern Med* 1985; 102: 164 – 168

26. Coenraad MJ, Meinders AE, Vandenbroucke JP, Frolich M, Taal JCW, Bolk JH. Causes of hyponatremia in the departments of internal medicine and neurosurgery. European Journal of Internal Medicine 2003; 14: 302 − 309.

PROFORMA

Name :

Age / Sex : IP No.

Address :

Vitals : PR : BP : RR :

Conscious / Unconscious

CNS

Infections / Metabolic

Vomiting :

Diarrhoea :

Pain :

Edema :

Anemia :

Thyroid swelling :

CCF :

CKD :

CLD :

Nephrotic Syndrome

Lung infections

Tumours

Drug Intake:

Carbamazepine

Phenothiazine

Tricyclic antidepressant

SSRI

Cyclophophamide

Vincristine

Diuretic

Mannitol

IV fluids

AGE	SEX	PR	BP	DIAR	VOMIT	PAIN	EDEMA	ANEMIA	THYROID	DRUGS	DIAG	IVF	DIURETIC	BS	UREA	Cr	Na	K	CORTISOL	URINE	OSMOLALITY
53	m	100	100/70					1			pneumonia			117	37	0.9	109	2.2	8.68	800	231
42	M	80	90/60			1					AGE	1		60	33	1.5	126	2.9	12.6	1000	261
40	F	86	140/80			1	1				FEVER	1		108	21	0.9	127	3.5	8	800	263
75	M	86	80/60		1	1		1			CKD		1	83	198	3.2	123	3.2	25.9 i	300	286
75	M	120	140/90				1	1			CKD		1	94	32	2.4	120	3.9	18 i	600	250
65	M	80	200/100					1			CVA		1	72	24	0.8	128	4.1	17 i	1000	264
43	M	86	100/70			1					CKD		1	89	18	0.9	128	3.9	6.6	600	264
40	M	137	100/70			1	1	1			CCF		1	101	75	1.2	127	4.7	34.3 i	600	273
60	M	72	100/70			1	1				CCF		1	73	44	1.2	129	3.4	16.5	800	270
55	M	90	110/70		1			1			CKD		1	117	230	8.2	125	5.8	28.5 i	100	297
40	M	80	180/100		1	1		1			CKD		1	80	209	8.8	127	4.8	8.13	800	296
58	M	82	130/70		1	1					CCF			112	20	0.7	128	4.2	6.9	1000	265
76	M	82	150/90					1			pneumonia			127	35	1	127	4.6	45.2 i	800	265
70	F	68	170/100		1	1	1	1			CNS tumour		1	114	42	0.9	120	3.6	16	800	254
48	F	86	150/100			1	1	1			SLE		1	112	85	4.2	112	3.6	10	400	245
65	M	82	140/90		1	1		1			AGE			93	31	1.3	116	6.1	11.6	600	242
80	F	80	140/80	1	1	1	1	1			CNS tumour			229	34	1	122	3.4	23.5 i	800	263
32	M	98	110/80			1					FEVER			65	16	0.9	120	3.9	19.4	1200	246
55	F	98	90/70	1			1				AGE			98	22	0.8	123	3.3	9.9	600	255
46	F	86	100/70								FEVER			91	15	0.7	129	3.5	8.9	1000	266
49	F	76	130/80				1				FEVER/DM			220	32	1	124	3.7	16	600	266
23	F	78	100/70				1	1			Aplastic Ane			136	17	0.7	120	3.5	0.8	600	250
77	M	86	160/80			1					Ca Lung			126	34	0.8	128	2.9	28.9 i	650	269
52	M	78	100/70				1	1			CLD	1		64	64	2.5	123	3.7	20 i	900	261
20	M	100	90/70		1		1	1			CLD			68	48	0.6	125	3.7	1.09	150	262
85	F	88	130/80		1		1	1			CKD			108	156	9.3	125	3.7	24.3 i	1200	283
65	F	76	130/70								LRTI			206	43	0.9	121	3.7	12.3	1000	242
58	F	84	210/110		1			1			CKD			60	101	3.4	129	6.9	12.8	600	279
35	F	90	140/100		1						CKD			81	112	3.4	114	4.2	21.2 i	800	252
39	M	96	120/80			1		1			PTB			83	25	0.7	121	3.6	16	700	251
45	M	76	190/100		1	1	1	1			CCF/CKD		1	193	253	17.6	123	4.9	63 i	700	301

58	F	96	120/90								LRTI			110	24	1	125	3.8	16.9 i	600	260
70	F	84	120/80			1	1				Ca Lung			201	19	0.9	125	3.3	15	800	264
31	M	80	140/70				1	1			CKD			128	73	2.3	125	5.6	15	600	270
70	M	100	190/90								COPD/SHT			68	58	1.3	126	4	25.4 i	1200	266
53	F	84	180/100		1	1	1				CKD			114	130	4.5	127	6	10.4	800	283
65	M	78	150/90								CVA		1	142	138	1.9	126	4.3	20.5	550	284
60	M	120	60/40					1			pneumonia			244	143	1.6	118	4.8	56 i	900	275
52	M	86	100/70			1	1				DM/UTI			354	34	1.1	115	3.3	23 i	600	256
70	M	125	110/70					1			COPD			182	59	1.9	127	4.4	9.25	800	275
52	M	110	90/60			1	1	1			PTB			98	37	0.8	118	3.6	23 i	800	248
21	F	80	130/90		1	1					OPC			67	16	0.6	126	3.1	8.5	1300	259
40	F	102	100/70	1	1						AGE			108	25	1.2	108	3.3	9	600	226
42	F	104	160/100				1				CCF		1	62	19	0.9	128	3.7	8.4	1000	262
55	M	102	100/70			1		1		CBZ	SEIZURES/DM			410	144	1.5	126	4.6	5.6	300	300
30	F	96	100/70								FEVER			108	35	1.2	128	3.5	16.2	1200	268
37	F	88	160/120			1	1	1			SLE/CKD		1	98	56	2	108	5	11.4	600	231
70	F	90	100/70				1				DCM			90	34	1.1	126	3.8	18.2	900	263
60	F	86	150/100		1		1	1			CKD			88	66	4	128	5.1	19.5	700	272
25	F	90	100/70		1						FEVER			86	20	0.8	128	3.6	13.7	1200	264